June 8, 2000

memo to: EPA Science Advisory Board Executive Committee

from: James D. Wilson, Senior Fellow

subject: Comment on "Use of data derived from the testing of human subjects."

I want to bring to your attention three issues raised by the recommendations appearing in the draft memo on this subject intended for the Administrator. Two of these are primarily issues of perception. The third concerns use of human data in safety evaluation; I suggest that the recommendation be broadened from its narrow focus on statistical design to include the broader question of how results of human studies can be used to evaluate safety of chemicals.

First, let me urge you to commend the SAB staff, and particularly Dr. Rondberg, for bringing about what appears to be a satisfactory resolution of significant differences of opinion among the panel. Clear traces of these differences can be discerned in the panel's report. One can only imagine the patience and tact required to find language acceptable to all sides.

Subcommittee finding d) voices an absolute, value-based prescription that the Executive Committee may not want to adopt. The words, "In no case should developing humans . . . be exposed to neurotoxic chemicals." seem much too broad to me. From the sentence following this one, I infer that the panel intended to express its opinion that the risks posed by clinical testing of potentially neurotoxic substances will always exceed any conceivable benefits. But this sentence goes much further. It connects an absolute ("in no case") with an undefinable ("neurotoxic chemicals"). Who identifies a "neurotoxic chemical?" By what authority? Is this to apply to substances that may have some potential for causing damage, under some circumstances (e.g., paint thinner)? Is it to be read as a policy judgment applicable, say, to regulation of hazardous air pollutants? The Executive Committee may want to suggest that the wording of this finding be refined and narrowed, better to fit the topic assigned to the panel.

Subcommittee finding f) 2) may suggest to a naïve reader that the panel would countenance poisoning farm workers in order not to place volunteers at any risk. This finding seems to me to express, in different words, the value that risks and benefits of clincal studies be given careful consideration, and in particular that if data are available from other sources, the benefits of clincal studies may become infinitesimal. There's not necessarily any harm in redundancy. However, this present sentence can be read to suggest that pesticide sponsors should prefer to use the public, or perhaps some fraction of it, as their guinea pigs. Perhaps the sentence might be rewritten to clarify its intent.

Subcommittee finding f) 5) is too narrow to serve the public interest. It would be of much greater value for the Agency to convene a workshop on methods for judging safety using human data, rather than

focus simply on statistical-design considerations. The issue of statistical power is raised in this report (Appendix B) in the context of identifying No Observed AdverseEffect Levels, a measure of toxicologic response used in evaluating safety of pesticide residues. It assumes that standards intended to protect the public will be set based on NOAEL values from human studies. EPA often does just this.

The Subcommittee Report (§§ 3.1 and 3.2.) inveighs at some length about the evils of doing tests designed to identify human NOAELs. This being the case, I wonder about the value to the public of devoting resources to a workshop intended to address statistical considerations of a kind of test the Agency has rejected.(1)

The Subcommittee may not know that there exist good reasons for EPA to abandon altogether the procedure it now uses for human data. This practice of dividing a human NOAEL by 10 (or some other arbitrary divisor) represents a truncation of the procedure long used for judging safety of food additives and pesticide residues, introduced in the mid-1950s by Lehman and his colleagues.(2) Lehman's procedure actually consists of a series of steps involving expert judgment, not just the NOAEL/100 step which receives most attention. This series of steps include a tuned set of biases intended to achieve a particular balance between risk and benefit.(3) In using the human-NOAEL/10 algorithm, EPA has made two errors. First, it discards the protective bias introduced by an instruction to "use the most sensitive study" (as toxicologists call it) as the basis for an RfD value. Second, it assumes to be true the fiction that Lehman's 100-fold safety factor can be reliably factored into two ten-fold ones, representing intra- and inter-species variability. In fact, preliminary results suggest that the greater part of the protective bias in Lehman's procedure occurs in the "most sensitive study" instruction. EPA has never, to my knowledge, published either a theoretical or empirical justification for the human-NOAEL/10 practice. The bottom line of all this is that we can not have confidence that EPA's practice adequately protects the public.

In addition, there are further reasons why a workshop on how to base safety evaluations on human data would be of public benefit. Lehman's procedure is limited by the need to be able to feed test animals at a rate 100 times or more the intended use level of the substance whose safety is to be evaluated. Studies in which the test substance comprises much more than 10% of an animal's diet are of dubious reliability, in the predictions they make concerning human response. Thus Lehman's procedure is not valid for substances which may make up a percent or so of the human diet. Substances that fall into this class include things intended to add fiber to the diet, some low-calorie sweeteners, and non-nutritive fat substitutes such as Procter & Gamble's "Olestra." In the last decade or so FDA has struggled to find an appropriate method to judge safety of these kinds of proposed food additives. I believe that FDA would welcome a chance to explore human-data based methods of testing safety.

Thus I urge the Executive Committee to broaden the Joint Subcommittee's recommendation, to recommend that EPA pursue a workshop on general methods to evaluate safety of chemicals in food that incorporate human data.

NOTES

1) J. Warrick, "U.S. rejects pesticide tests on humans." The Washington Post, Weds., June 7, 2000, p.A2.

2) A. J. Lehman and O. G. Fitzhugh, "100-Fold margin of safety." Association of Food and Drug Officers of the United States Quarterly Bulletin 18, 33-35 (1954).

3) R. M. Putzrath and J. D. Wilson, "Fundamentals of health risk assessment. Use, derivation, validity and limitations of safety indices." Risk Anal. 19: 231-247 (1999).